SYNTHESIS OF 1-SUBSTITUTED DIHYDROPYRIMIDINONE AND QUINAZOLINONE DERIVATIVES

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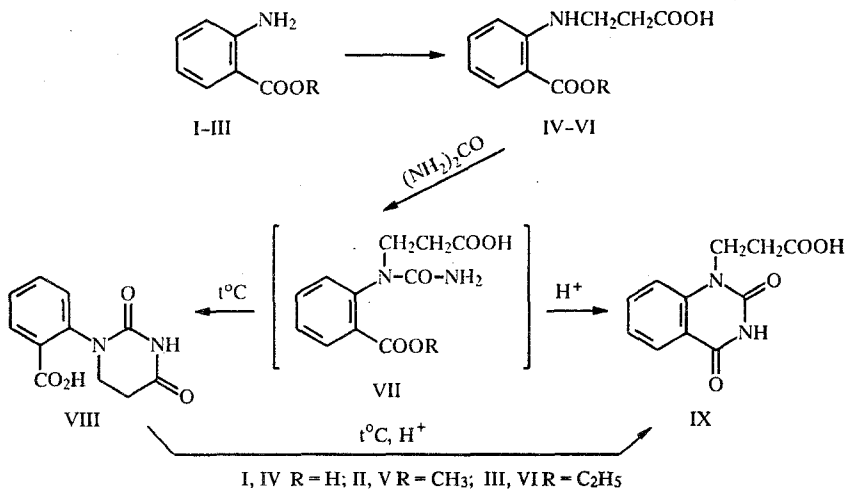
Condensation of N-substituted β-alanines (synthesized from anthranilic acid or its esters and acrylic acid) with urea afforded the corresponding 1-substituted dihydropyrimidinedione and quinazolinedione. When potassium thiocyanate was employed in the reaction instead of urea, decarboxylation and desulfuration occurred.

The reaction of N-(2-hydroxyphenyl)-β-alanines with urea yields either five-membered or six-membered nitrogen-containing heterocyclic compounds, depending on the conditions [1]. Following on research into the synthesis of heterocyclic compounds based on N-substituted β-amino acids, we investigated the condensation of N-(2-carboxyphenyl)-, N-(2-methoxycarbonylphenyl)- and N-(2-ethoxycarbonylphenyl)-β-alanines with urea and potassium thiocyanate.

The N-substituted β-alanines IV-VI used initially were obtained by boiling anthranilic acid or its esters (I-III) with acrylic acid in toluene. When compounds IV-VI were condensed with urea in boiling acetic acid, a mixture of 1-(2-carboxyphenyl)dihydro-2,4(1H, 3H)-pyrimidinedione (VIII) and 1-carboxyethylquinazoline-2,4(1H, 3H)-dione (IX) was seen to form, with the latter compound predominating. In the condensation process corresponding N-carbamoyl-β-alanines are formed as intermediates; on heating in the presence of mineral acids these cyclize into dihydropyrimidinedione derivatives [2-5].



I, IV R = H; II, V R = CH_3; III, VI R = C_2H_5

In this particular case the intermediate N-(2-carboxyphenyl)-N-carbamoyl-β-alanine (VII) is probably an unstable substance which undergoes both thermal and acid-catalyzed cyclization. Quinazolinedione IX is more stable than dihydropyrimidinedione VIII, a fact that is lent support by their ratio in the reaction mixture and by subsequent investigations. When β-alanines IV-VI were fused with urea at 160°C dihydropyrimidinedione VIII was formed as the main product. As pointed out above, condensation in acetic acid produced a mixture of compounds VIII and IX, but when sulfuric acid was added at the end of the reaction, only quinazolinedione IX was isolated from the reaction mixture. In this instance the direct formation

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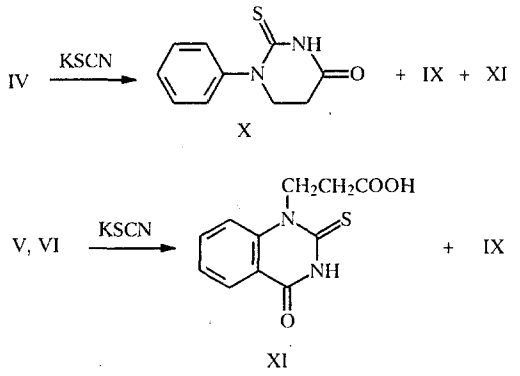
of quinazolinedione IX is accompanied by the recyclization of 1-(2-carboxyphenyl)dihydro-2,4(1H, 3H)-pyrimidinedione into the same product. This phenomenon was corroborated by the recyclization of pure dihydropyrimidinedione VIII by heating in hydrochloric acid. The structure of isomeric compounds VIII and IX was determined from PMR spectral data and from the difference in their chemical properties. In the PMR spectra of the two isomers the $N-CH_2-CH_2$ fragment proton signals for quinazolinedione IX are found in a weaker field than the cyclic system proton signals for dihydropyrimidinedione VIII, which is typical of acyclic compounds. Dissolving compound VIII in bases led to the decomposition of the dihydropyrimidinedione ring into the corresponding N-carbamoyl-β-alanine, while quinazolinedione IX was only transformed into the corresponding salt under these conditions.



Boiling β-alanine IV with potassium thiocyanate in acetic acid yielded a mixture of three products, namely 1-phenyldihydro-4(1H, 3H)-pyrimidinone-2-thione (X), quinazolinedione IX and quinazolinone-2-thione XI, which from PMR spectral data were found in a ratio of 9:4:3. Compound X was isolated by fractional crystallization. Addition of hydrochloric acid at the end of the reaction had no effect on the qualitative composition of the product mixture. No decarboxylation was observed in the reaction between β-alanine V or VI and the blocked carboxyl group; two products were isolated from the reaction mixture: 1-carboxyethylquinazoline-4(1H, 3H)-one-2-thione (XI) and quinazolinedione IX, whose ratio was determined from the difference in $N-CH_2$ group chemical shifts in the PMR spectra. The $N-CH_2$ group proton signals in the PMR spectrum of compound IX were observed in the form of a triplet centered around 2.25 ppm, while in the PMR spectrum of its 2-thio analog the same signals were shifted 0.42 ppm downfield.

EXPERIMENTAL

The PMR spectra were taken on a Bruker WM-360 spectrometer (cpds. VIII, IX) and Tesla BS 487C, internal standard TMS. Mass spectra were recorded using a Hitachi M-80A double focusing spectrometer with 20 eV ionizing electron energy and with direct sample insertion into the ion source. The reaction course and the purity of the synthesized compounds were monitored by means of TLC on Silufol UV-254 plates in acetone–hexane (3:1) and ether–hexane (8:1) systems, developing in UV light or with iodine.

Elemental analysis data on C, H, and N were in line with calculated values.

N-(2-Carboxyphenyl)-β-alanine (IV, $C_{10}H_{14}NO_4$). A mixture of 27.4 g (0.2 mole) of anthranilic acid (I) and 14.9 g (0.2 mole) of acrylic acid in 40 ml of toluene was boiled for 10 h, then left to stand for 12 h at 4°C. The resultant precipitate of IV was filtered off and washed with toluene and hexane. Yield 31.2 g (74.6%), mp 176-177°C (from ethanol). From literature data [6] mp 172-172.5°C. PMR spectrum ($(CD_3)_2CO$): 2.55 (2H, t, α-CH_2), 3.47 (2H, t, β-CH_2), 6.4-8.0 (4H, m, arom. H), 8.0-8.8 ppm (2H, broad s, N^+H_2).

N-(2-Methoxycarbonylphenyl)-β-alanine (V, $C_{11}H_{13}NO_4$). As with the synthesis of compound IV, from 30.3 g (0.2 mole) of methyl anthranilate (II) and 14.2 g (0.2 mole) of acrylic acid. Yield 29.9 g (67%), mp 99-100°C (from toluene). PMR spectrum ($(CD_3)_2CO$): 2.51 (2H, t, α-CH_2), 3.40 (2H, t, β-CH_2), 3.67 (3H, s, OCH_3), 6.4-7.9 ppm (4H, m, arom. H).

N-(2-Ethoxycarbonylphenyl)-β-alanine (VI, $C_{12}H_{15}NO_4$). As with the synthesis of compound IV, from 33 g (0.2 mole) of ethyl anthranilate (III) and 14.2 g (0.2 mole) of acrylic acid. Yield 29.1 g (61.3%), mp 104-105°C (from toluene). PMR spectrum (CF_3COOH): 1.06 (3H, t, $CH_2C\underline{H}_3$), 2.72 (2H, t, α-CH_2), 3.53 (2H, t, β-CH_2), 4.17 (2H, qu, $C\underline{H}_2CH_3$), 7.2-8.1 ppm (4H, m, arom. H).

1-(2-Carboxyphenyl)dihydro-2,4(1H, 3H)-pyrimidinedione (VIII, $C_{11}H_{10}N_2O_4$). A. A mixture of 4.2 g (0.02 mole) of β-alanine IV and 6 g (0.1 mole) of urea was heated at 160°C for 8 h; then 75 ml of water was carefully added to the mixture, which was left for a further 4 h at 20°C. The starting reagents were removed from the resultant precipitate VIII by boiling for 1 min in 20 ml of ethanol. The hot mixture was filtered and the crystals of VIII were washed with 10 ml of ethanol. Yield 2.06 g (44%), mp 266-268°C (from CH_3COOH). PMR spectrum (DMSO-D_6): 2.47(2H, d, 5-CH_2), 4.20 (2H, t, 6-CH_2), 6.94 (1H, s, OH), 7.1-8.7 (4H, m, arom. H), 9.07 ppm (1H, s, NH). Mass spectrum, m/z (I%): 234 ($13M^+$), 233 (16), 198 (44), 162 (100), 146 (35), 145 (24), 132 (62), 129 (42), 92 (12), 72 (21).

B. As with method A, from 4.48 g (0.02 mole) of β-alanine V and 6 g (0.1 mole) of urea. Yield 1.53 g (32.7%).

C. As with method A, from 4.74 g (0.02 mole) of β-alanine VI and 6 g (0.1 mole) of urea. Yield 2.2 g (47%).

1-Carboxyethylquinazoline-2,4(1H, 3H)-dione (IX, $C_{11}H_{10}N_2O_4$). A. A mixture of 10.5 g (0.05 mole) of β-alanine IV, 6 g (0.1 mole) of urea and 30 ml of glacial acetic acid was boiled for 14 h. After 15 ml of conc. HCl had been added, the mixture was boiled for a further 10 min, diluted with 50 ml of water, and left to stand for 3 h at 20°C. The resultant precipitate of compound IX was filtered off and washed with water. Yield 7.74 g (66.1%), mp 235-237°C (from CH_3COOH). PMR spectrum (DMSO-D_6): 2.59 (2H, t, α-CH_2), 4.25 (2H, t, β-CH_2), 7.2-8.1 (4H, m, arom. H), 11.52 (1H, s, NH), 12.38 ppm (1H, broad s, OH). Mass spectrum, m/z (I%): 234 ($38M^+$), 188 (22), 180 (11), 162 (100), 146 (21), 145 (13), 132 (87), 119 (83), 92 (36), 91 (11), 72 (30), 55 (23), 27 (20).

B. As with method A, from 11.2 g (0.05 mole) of β-alanine V and 6 g (0.1 mole) of urea. Yield 9.1 g (77.7%).

C. As with method A, from 11.8 g (0.05 mole) of β-alanine VI and 6 g (0.1 mole) of urea. Yield 6.1 g (52.1%).

D. A mixture of 0.47 g (2 mole) of dihydropyrimidinedione VIII and 6 ml of 10% sodium hydroxide solution was heated to boiling, then left for 30 min at 20°C. The solution was acidified with conc. HCl to pH 1, and the resulting precipitate IX was filtered off and washed with water. Yield 0.41 g (87.2%).

E. A mixture of 0.47 g (2 mmole) of dihydropyrimidinedione VIII and 5 ml of conc. HCl was boiled for 5 min; the liquid fractions were driven off in vacuum, giving compound IX in quantitative yield.

1-Phenyldihydro-4(1H, 3H)-pyrimidinone-2-thione (X, $C_{10}H_{10}N_2OS$), Quinazolinedione IX, and Quinazolinone-2-thione (XI, $C_{11}H_{10}N_2OS$). A mixture of 4.2 g (0.02 mole) of β-alanine IV and 3.9 g (0.04 mole) of potassium thiocyanate in 20 ml of acetic acid was boiled for 10 h. After 20 ml of 18% hydrochloric acid had been added, boiling was continued for a further 30 min, then the mixture was diluted with 20 ml of water. The precipitate that resulted from 12 h standing at 20°C (a mixture of compounds X, IX, and XI) was filtered off and washed with water. Yield 1.51 g. From PMR spectral data the ratio of compounds X, IX, and XI was 9:4:3.

1-Phenyldihydro-4(1H, 3H)-pyrimidinone-2-thione (X) was isolated from the mixture by fractional crystallization from ethanol, mp 185-186°C (from ethanol). From literature data, mp 186.5-187°C (from dioxane). PMR spectrum (DMSO-D_6): 2.82 (2H, t, 5-CH_2), 3.90 (2H, t, 6-CH_2), 7.2-7.6 (5H, m, arom. H), 11.23 ppm (1H, s, NH).

1-Carboxyethyl-4(1H, 3H)-quinazolinone-2-thione (XI) and Compound IX. A. A mixture of 4.5 g (0.02 mole) of alanine, 3.9 g (0.04 mole) of potassium thiocyanate, and 20 ml of glacial acetic acid was boiled for 10 h. After adding 20 ml of 18% hydrochloric acid, the mixture was boiled for a further 30 min, then diluted with 20 ml of water. The resultant crystals of compounds XI and IX were filtered off and washed with water. Mixture yield 2.1 g. From PMR spectral data, the ratio of IX and XI in the mixture ~2:1.

B. As with method A, from 4.74 g (0.02 mole) of β-alanine VI and 3.9 g (0.04 mole) of potassium thiocyanate. Mixture yield 2.38 g; from PMR spectral data, ratio of IX to XI ~2:1.

Compound XI obtained from the mixture by method B was isolated by passing it through a column containing silica get L 40/100, eluting with an ether–hexane mixture (8:1), and taking off the R_f 0.54 fraction; mp 203-204°C (from ethanol). PMR spectrum (CF_3COOH): 2.67 (2H, t, α-CH_2), 4.67 (2H, t, β-CH_2), 6.8-8.1 ppm (4H, m, arom. H).

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